General

Guideline Title

Neoadjuvant or adjuvant therapy for resectable gastric cancer.

Bibliographic Source(s)

Knight G, Earle CC, Cosby R, Coburn N, Youssef Y, Spithoff K, Malthaner R, Wong RKS, Gastrointestinal Cancer Disease Site Group. Neoadjuvant or adjuvant therapy for resectable gastric cancer. Toronto (ON): Cancer Care Ontario (CCO); 2011 Apr 5. Various p. (Evidence-based series; no. 2-14). [147 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Gastrointestinal Cancer Disease Site Group. Earle CC, Maroun J, Zuraw L. Neoadjuvant or adjuvant therapy for resectable gastric cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 May 21 [online update]. 21 p. (Practice guideline; no. 2-14).

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

- Postoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) based on the Macdonald approach (see Section 2A, Appendix 6 in the original guideline document) or perioperative epirubicin/cisplatin/5-FU (ECF) chemotherapy based on the Cunningham/Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) approach (see Section 2A, Appendix 6 in the original guideline document) are both acceptable standards of care. Choice of treatment should be made on a case-by-case basis.
- Adjuvant chemotherapy is a reasonable option for those patients for whom the Macdonald and MAGIC protocols are contraindicated.
- Patients with resectable gastric cancer should undergo a pre-treatment multidisciplinary assessment to determine the best plan of care. In addition to surgery, all patients should be considered for neoadjuvant and/or adjuvant therapy.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Potentially curable, surgically resectable (stage 1B [invasion of the muscularis propria] and above) gastric cancer

Guideline Category

Assessment of Therapeutic Effectiveness

Evaluation

Treatment

Clinical Specialty

Gastroenterology

Internal Medicine

Oncology

Radiation Oncology

Surgery

Intended Users

Physicians

Guideline Objective(s)

To evaluate whether patients with resectable gastric cancer (stage 1B [invasion of the muscularis propria] and above) should receive neoadjuvant or adjuvant therapy in addition to surgery

Target Population

Adult patients with potentially curable, surgically resectable (stage 1B [invasion of the muscularis propria] and above) gastric cancer

Interventions and Practices Considered

1. Postoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) or perioperative epirubicin/cisplatin/5-FU (ECF) chemotherapy
2. Adjuvant chemotherapy
3. Pre-treatment multidisciplinary assessment

Major Outcomes Considered

- Overall survival (OS)

- Disease-free survival (DFS)
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategy

The MEDLINE (January 2002 to June week 3 2010), EMBASE (2002 to 2010 week 25), and Cochrane Library (February 2010), databases were systematically searched using revised literature search strategies (see Appendix 1 in the original guideline document). In MEDLINE, the Medical Subject Heading (MeSH) "stomach neoplasms" and associated text words were combined with treatment-related terms, including the MeSH terms "chemotherapy, adjuvant," "radiotherapy, adjuvant," and "neoadjuvant therapy" and the text words "adjuvant," "neoadjuvant," "preoperative," and "postoperative." These terms were then combined with a search filter designed to identify randomized trials, systematic reviews, and meta-analyses adapted from a strategy developed by the Scottish Intercollegiate Guidelines Network (SIGN), available at www.sign.ac.uk. Modifications were made to the search terms, where appropriate, for use in EMBASE. The proceedings of the 2002 to 2010 American Society of Clinical Oncology (ASCO) and the 2002 to 2009 American Society for Therapeutic Radiology and Oncology (ASTRO) annual meetings were also searched for abstract reports of relevant studies. Reference lists of relevant reviews were searched for additional relevant reports.

Study Selection Criteria

The study inclusion and exclusion criteria used in the original systematic review (see Section 2B in the original guideline document) were modified for the updated review. Articles were selected for inclusion if they:

- Were published abstracts or fully published reports of randomized controlled trials (RCTs) comparing preoperative or postoperative chemotherapy and/or radiotherapy versus potentially curative surgery alone or another preoperative or postoperative therapy approach. Syntheses of RCTs in the form of systematic reviews or meta-analyses were also included.
- Were studies of adults with resectable gastric cancer. Trials of gastric cancer that also including patients with tumours of the gastroesophageal junction were included.
- Included reports of overall survival (OS) data.

Articles were excluded if they:

- Were studies of immunotherapy, immunochemotherapy, intraperitoneal chemotherapy, or intra-arterial chemotherapy.
- Were published in a language other than English, due to unavailability of translation services.
- Were abstract reports of preliminary or interim data only.
- Were abstract reports of studies that were subsequently fully published.
- Reported results of RCTs or meta-analyses in the form of a letter or editorial.
- Included a majority of patients with esophageal tumours and did not report data separately for patients with gastric or gastroesophageal junction (GEJ) tumours.

Number of Source Documents

Overall, 22 randomized controlled trials (RCTs), 13 meta-analyses, and two secondary analyses that report survival data are included in this systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Study Quality Appraisal

The quality of the systematic reviews and meta-analyses was assessed using the A Measurement Tool to Assess Systematic Reviews (AMSTAR) tool. Randomized trials were assessed for key methodological characteristics, using information provided in the trial reports. The following elements were assessed: generation of allocation sequence, allocation concealment, blinding, intention-to-treat analysis, withdrawals, loss to follow-up, funding source, statistical power calculations, length of follow-up, differences in baseline patient characteristics, and early termination.

Synthesizing the Evidence

No data pooling was conducted in this review due to the availability of published meta-analyses comparing postoperative chemotherapy to surgery alone, postoperative chemoradiotherapy (CRT) to either surgery alone or postoperative chemotherapy, and preoperative radiotherapy to surgery alone.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Methods

The Evidence-Based Series (EBS) guidelines developed by Cancer Care Ontario Program in Evidence-based Care (CCO PEBC) use the methods of the Practice Guidelines Development Cycle. For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by one member of the PEBC Gastrointestinal Disease Site Group (DSG) and a methodologist.

The systematic review is a convenient and up-to-date source of the best available evidence on neoadjuvant or adjuvant therapy for resectable gastric cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trial (RCT) data and meta-analyses of RCTs. That evidence forms the basis of the recommendations developed by the Gastrointestinal DSG. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada.

Development and Internal Review

This guideline is an update of EBS #2-14, which was originally developed in 2000 and then updated in 2003. The Gastrointestinal DSG believed that this further update was warranted, given the existence of new evidence published that could change the recommendations provided in the previous guideline.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Report Approval Panel (RAP)

Prior to the submission of this Evidence-Based Series (EBS) draft report for external review, the report was reviewed and approved by the Program in Evidence-based Care (PEBC) RAP, which consists of two members, including an oncologist, with expertise in clinical and methodology issues.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and the review and approval of the report by the PEBC RAP, the Gastrointestinal (GI) DSG circulated Sections 1 and 2 of the original guideline document to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, three targeted peer reviewers from Ontario and the United States considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. The three reviewers agreed, and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on October 20, 2010. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The GI DSG reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All medical oncologists, radiation oncologists and surgical oncologists from Ontario in the PEBC database were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1 in the original guideline document) and the evidentiary base (Section 2 in the original guideline document). The notification email was sent on October 26, 2010. The consultation period ended on December 14, 2010. The GI DSG reviewed the results of the survey.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the GI DSG and the

Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the question of interest emerges.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized controlled trials, meta-analyses, and secondary analyses.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Two secondary analyses of the Southwestern Oncology Group (SWOG)/Intergroup trial were identified that reported updated survival data. These results are consistent with earlier data reported in Section 2B of the original guideline document. Updated results from Hundahl indicated a median survival of 36 months for patients who received postoperative chemoradiotherapy (CRT) (5-fluorouracil [5-FU]/Leucovorin) vs. 27 months for patients who underwent surgery alone (p=0.003). Relapse-free survival was 30 months vs. 19 months (p<0.001). A further update of this trial demonstrates that the original SWOG/Intergroup trial results reported in 2001 are robust with almost identical results, even with more than 11 years of follow-up for both overall survival (OS) (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63 to 0.92; p=0.005) and disease-free survival (DFS) (HR, 0.66; 95% CI, 0.55 to 0.80; p<0.001), favouring postoperative CRT over surgery alone.
- The Cunningham/Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial is the largest trial incorporating preoperative therapy to date and the only randomized trial with a perioperative approach. A significant benefit for perioperative epirubicin/cisplatin/5-FU (ECF) was reported for OS (HR, 0.75; 95% CI, 0.60 to 0.93; p=0.009) and progression-free survival (PFS) (HR, 0.66; 95% CI, 0.53 to 0.81; p<0.001).
- A meta-analysis by Fiorica of five trials that provided 3-year mortality data indicated a non-significant benefit for postoperative CRT over surgery (odds ratio [OR], 0.79; 95% CI, 0.59 to 1.05; p=0.10). However, the meta-analysis of three trials that provided 5-year mortality data indicated a significant benefit for postoperative CRT over surgery (OR, 0.45; 95% CI, 0.32 to 0.64; p<0.00001).
- An individual patient data meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group found a modest advantage for postoperative chemotherapy for OS (HR, 0.82; 95% CI, 0.76 to 0.90; p<0.001) and for DFS (HR, 0.82; 95% CI, 0.75 to 0.90; p<0.001).

Potential Harms

- Many of the adjuvant regimens reported in the literature have caused significant treatment-related morbidity and even death. Chemotherapy in particular can cause hematological toxicity, infections, and gastrointestinal side effects, as described with combined chemoradiotherapy.
- For patients with borderline renal function, radiation is expected to be associated with an increased risk of chronic renal impairment.

Contraindications

Contraindications

The presence of cardiac or renal dysfunction would contraindicate the use of epirubicin and cisplatin, respectively.

Qualifying Statements

Qualifying Statements

- The Macdonald and Cunningham/Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) protocols have never been compared to each other in a single trial to determine if one is superior to the other.
- The mix of tumour sites in the Macdonald and MAGIC protocols were not the same. In the MAGIC trial, 74% of participants had a stomach tumour, 11.5% had a gastroesophageal junction (GEJ) tumour, and 14.5% had a lower esophageal tumour. In the Macdonald trial, most participants had a tumour in the distal stomach. However, approximately 20% of participants had lesions present in the GEJ. There were no esophageal tumours.
- The Boige et al. study comparing preoperative 5-fluorouracil (5-FU)/cisplatin vs. surgery alone demonstrated a significant improvement in overall survival (OS) and disease-free survival (DFS) with preoperative chemotherapy. Since these data are currently only available in abstract form, the Gastrointestinal Disease Site Group (Gastrointestinal DSG) does not recommend this treatment at this time. However, should these stated benefits be maintained when published in full and there are no material differences in reported toxicities, the DSG would consider recommending the Boige protocol in patients with resectable gastric cancer.
- Technical considerations pertaining to the delivery of radiation therapy are provided in the Discussion in Section 2A of the original guideline document.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2000 Dec 6 (revised 2011 Apr 5)

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Guideline Committee

Gastrointestinal Cancer Disease Site Group

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

Gastrointestinal Cancer Disease Site Group (GI DSG) members involved in the development of the systematic review and clinical practice guideline were polled for potential conflicts of interest. All authors declared no conflicts of interest.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Neoadjuvant or adjuvant therapy for resectable gastric cancer. Summary. Toronto (ON): Cancer Care Ontario; 2011 Apr 5. 6 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site .
- Program in Evidence-Based Care (PEBC) handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available in PDF from the CCO Web site.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on June 23, 2003. The information was verified by the guideline developer as of July 16, 2003. This summary was updated by ECRI on January 23, 2004. The information was verified by the guideline developer as of February 23, 2004. This NGC summary was updated by ECRI Institute on September 6, 2013.

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